TABLE 15-10. (continued)

Adjusted Exposure Index for Cardiovascular Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
			Low	Medium	High			
Femoral Pulses	Officer	n	—	—	—	Overall		—
						M vs. L	—	—
						H vs. L	—	—
	Enlisted Flyer	n	50	52	50	Overall		0.208
						M vs. L	2.15 (0.19,24.79)	0.542
						H vs. L	5.32 (0.59,47.78)	0.136
	Enlisted Groundcrew	n	131	140	117	Overall		0.576
						M vs. L	0.80 (0.13,5.01)	0.810
						H vs. L	0.32 (0.03,3.25)	0.337
Popliteal Pulses	Officer	n	—	—	—	Overall		—
						M vs. L	—	—
						H vs. L	—	—
	Enlisted Flyer	n	50	52	50	Overall		0.419
						M vs. L	1.04 (0.14,7.93)	0.968
						H vs. L	2.59 (0.47,14.30)	0.276
	Enlisted Groundcrew	n	131	140	117	Overall		0.490
						M vs. L	1.04 (0.29,3.68)	0.960
						H vs. L	0.46 (0.11,2.02)	0.308

TABLE 15-10. (continued)

Adjusted Exposure Index for Cardiovascular Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
			Low	Medium	High			
Dorsalis Pedis Pulses	Officer	n	113	110	102	Overall		0.535
						M vs. L	0.59 (0.23,1.51)	0.271
						H vs. L	0.82 (0.34,1.98)	0.667
	Enlisted Flyer	n	50	52	50	Overall		0.894
						M vs. L	1.04 (0.37,2.91)	0.944
						H vs. L	1.25 (0.46,3.38)	0.660
	Enlisted Groundcrew	n	130	140	117	Overall		0.613
						M vs. L	0.96 (0.46,1.97)	0.904
						H vs. L	0.69 (0.32,1.52)	0.358
Posterior Tibial Pulses	Officer	n	—	—	—	Overall		—
						M vs. L	—	—
						H vs. L	—	—
	Enlisted Flyer	n	50	52	50	Overall		0.746
						M vs. L	1.00 (0.17,6.00)	0.999
						H vs. L	1.68 (0.35,8.07)	0.516
	Enlisted Groundcrew	n	128	134	112	Overall		0.831
						M vs. L	0.60 (0.10,3.42)	0.562
						H vs. L	0.90 (0.20,4.00)	0.897

TABLE 15-10. (continued)

Adjusted Exposure Index for Cardiovascular Variables by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Exposure Index Medium	Exposure Index High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Leg Pulses	Officer	n	105	107	96	Overall		0.630
						M vs. L	0.89 (0.40,2.00)	0.779
						H vs. L	0.65 (0.27,1.60)	0.352
	Enlisted Flyer	n	49	52	48	Overall		0.475
						M vs. L	1.06 (0.38,2.95)	0.912
						H vs. L	1.70 (0.66,4.35)	0.271
	Enlisted Groundcrew	n	128	133	110	Overall		0.719
						M vs. L	1.08 (0.54,2.16)	0.826
						H vs. L	0.80 (0.38,1.68)	0.555
Peripheral Pulses	Officer	n	105	107	96	Overall		0.630
						M vs. L	0.89 (0.40,2.00)	0.779
						H vs. L	0.65 (0.27,1.60)	0.352
	Enlisted Flyer	n	49	52	48	Overall		0.475
						M vs. L	1.06 (0.38,2.95)	0.912
						H vs. L	1.70 (0.66,4.35)	0.271
	Enlisted Groundcrew	n	128	133	110	Overall		0.683
						M vs. L	1.01 (0.51,2.00)	0.976
						H vs. L	0.75 (0.36,1.57)	0.447

TABLE 15-10. (continued)

Adjusted Exposure Index for Cardiovascular Variables by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Exposure Index Medium	Exposure Index High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
All Pulses	Officer	n	104	107	96	Overall		0.616
						M vs. L	0.88 (0.39,1.98)	0.764
						H vs. L	0.65 (0.26,1.58)	0.337
	Enlisted Flyer	n	49	52	48	Overall		0.475
						M vs. L	1.06 (0.38,2.95)	0.912
						H vs. L	1.70 (0.66,4.35)	0.271
	Enlisted Groundcrew	n	128	133	110	Overall		0.683
						M vs. L	1.01 (0.51,2.00)	0.976
						H vs. L	0.75 (0.36,1.57)	0.447

*No conditions reported that were not verified; therefore, reported and verified analyses are the same.

—Adjusted relative risk not applicable for continuous analysis of a variable; adjusted analysis not performed due to sparse cells.

**Exposure index-by-covariate interaction ($0.01<p\leq0.05$)—adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

category, none of the differences, either unadjusted or adjusted, was statistically significant. The percent of individuals with hypertension in the medium exposure level category was similar to that in the low exposure category for each occupational stratum.

Reported and Verified Heart Disease

There were no statistically significant differences in the percentage of individuals with reported or verified heart disease for any occupational stratum in the unadjusted analyses. Differences were also nonsignificant in the adjusted analyses with the exception of the officer cohort, where the adjusted relative risk for the medium versus low contrast was significantly less than 1 (Adj. RR: 0.52, 95% C.I.: [0.30,0.90], p=0.019). The high versus low exposure level relative risk in the officers was also less than 1 and of borderline significance (p=0.082).

Reported and Verified Myocardial Infarction

There were no statistically significant differences, either unadjusted or adjusted, in any of the occupational strata.

Physical Examination Variables: Central Cardiac Function

Systolic Blood Pressure

In the officers and enlisted groundcrew, neither the mean values nor the percentage with abnormal blood pressure was significantly different across the three exposure levels (unadjusted or adjusted for covariates). In the enlisted flyers, however, there was a significant difference in the means that was consistent with a dose-response relationship: mean systolic blood pressures were 124.14, 128.79, and 133.55 in the low, medium, and high exposure level categories, respectively (p=0.037). The high versus low contrast was significant (p=0.010). After adjustment for covariates, however, the differences were still consistent with a dose-response relationship, but no longer statistically significant (p=0.181).

The percent with abnormal systolic blood pressure (>140 mm Hg) also increased with increasing exposure level, but did not reach statistical significance, either unadjusted or adjusted for covariates.

Heart Sounds

There were no statistically significant differences in abnormal heart sounds, either unadjusted or adjusted.

ECG-Overall

There were no statistically significant differences in overall ECG findings, either unadjusted or adjusted.

RBBB

There were only four individuals with RBBB--one officer, two enlisted flyers, and one enlisted groundcrew--and no significant exposure level effects. Adjusted analyses were not performed due to the small number of abnormalities.

LBBB

Only one Ranch Hand, an officer in the medium exposure level category, was found to have LBBB. Statistical analyses could therefore not be conducted.

Nonspecific T-Waves

There were no statistically significant differences, unadjusted or adjusted, for nonspecific T-wave findings in the officers or enlisted groundcrew. In the unadjusted analysis of the enlisted flyer cohort there was a borderline significant difference overall ($p=0.075$), with a significantly higher risk in the medium exposure level category as compared to the low exposure level category (Est. RR: 3.51, 95% C.I.: [1.05,11.73], $p=0.041$). This difference was of borderline significance after adjustment for covariates ($p=0.063$).

Bradycardia

There were no statistically significant differences in the occurrence of bradycardia in any of the three occupational strata in unadjusted analyses. The presence of bradycardia decreased with increasing exposure level in each occupational stratum.

Adjusted analyses did not detect significant exposure level effects in the enlisted flyers or enlisted groundcrew, but in the officers, there was a statistically significant exposure index-by-cholesterol-HDL ratio interaction ($p=0.045$). Appendix L, Table L-4, shows that there were fewer abnormalities in the medium and high exposure level categories as compared to the low exposure level category for individuals with ratios of at most 4.2 and for individuals with ratios between 4.2 and 5.5; whereas, in individuals with cholesterol-HDL ratios above 5.5, there were slightly more abnormalities in the medium and high exposure level categories as compared to the low exposure level category. The numbers were quite sparse, however. Table 15-10 also presents the results after deleting the interaction term from the model. The adjusted relative risks did not reach statistical significance.

Tachycardia

There were no cases of tachycardia among the Ranch Hands and stratified analyses were not performed.

Arrhythmia

There were no significant differences among the three exposure level categories, unadjusted or adjusted, in the presence of arrhythmia for either the officers or enlisted groundcrew. However, in the enlisted flyers, there was a statistically significant effect, with arrhythmia detected in six (11.8%) of the individuals in the high exposure level category, as compared to none in the low and none in the medium exposure level categories. The high versus low contrast is significant (p=0.025, Fisher's exact test). The number of abnormalities was too few for adjusted analyses.

ECG-Other Diagnoses

No significant differences emerged in the unadjusted analyses for any of the occupational strata, nor in the adjusted analyses for the enlisted flyers or enlisted groundcrew. There was, however, a statistically significant exposure index-by-age interaction in the officers (p=0.018). Upon stratification by age (Appendix L, Table L-4), there was an inverse dose-response relationship in those born in or after 1942, little difference among exposure level categories in those born between 1923 and 1941, and only four abnormalities in those born in or before 1922, all in the medium exposure level category. None of these within-stratum differences was statistically significant. After deleting the interaction term from the model (Table 15-10), the adjusted relative risks in the officers were not statistically significant.

Physical Examination Variables: Peripheral Vascular Function

Diastolic Blood Pressure

In the officers, there were no statistically significant differences in the mean diastolic blood pressure, either unadjusted or adjusted for covariates. The discrete analyses, however, detected a significantly greater percentage of abnormalities in the high exposure level category (p=0.039), which remained significant after covariate adjustment (Adj. RR: 5.53, 95% C.I.: [1.12,27.36], p=0.036). Those in the medium exposure level category did not exhibit an excess risk.

There were no significant differences, unadjusted or adjusted, in either the mean levels or the percent abnormal in the enlisted flyers.

In the enlisted groundcrew, there were no significant differences in the unadjusted continuous or discrete analyses, nor in the adjusted discrete analysis. The adjusted continuous analysis did reveal a significant exposure index-by-personality type interaction (p=0.012), which is examined more fully in Appendix L, Table L-4. This table shows that there was no significant difference in the exposure level means among those with Type A personalities; in Type B individuals, there was a significant difference (p=0.020), although not consistent with a dose-response relationship (adjusted means were 76.90, 80.52, and 76.80 in the low, medium, and high exposure level categories, respectively). Since the interaction did not reach the 1 percent significance level, Table 15-10 also presents the results after deletion of the interaction term from the model. The adjusted means could not be significantly different.

Funduscopic Examination

There were few funduscopic abnormalities and no evidence of exposure level effects. Adjusted analyses could not be performed on this variable.

Carotid Bruits

Again, there were few abnormalities and no significant differences among the exposure level groups. Adjusted analyses could not be performed on this variable.

Radial Pulses

Only two Ranch Hands had radial pulse abnormalities, both in the low exposure category. Adjusted analyses were not possible.

Femoral Pulses

There were no significant differences, unadjusted or adjusted, in femoral pulse abnormalities. There was a trend consistent with a dose-response relationship in the enlisted flyers, but it was not statistically significant. Analyses in the other occupational categories were unremarkable.

Popliteal Pulses

There were no statistically significant differences, unadjusted or adjusted, in the percentage of individuals with popliteal pulse abnormalities in the three exposure level categories for any of the occupational strata.

Dorsalis Pedis Pulses

No statistically significant differences were detected, unadjusted or adjusted, in any of the occupational strata.

Posterior Tibial Pulses

No significant differences were found.

Leg Pulses

For the aggregated variable combining all leg pulses, there were no significant differences, either unadjusted or adjusted for covariates.

Peripheral Pulses

The analysis of all peripheral pulses gave similar results to that for the leg pulses, i.e., no significant differences among the three exposure

level categories within any occupational stratum, either unadjusted or adjusted for covariates.

All Pulses

Analysis of the aggregated index of all pulses did not reveal significant differences, either unadjusted or adjusted, for any of the occupational strata.

Exposure Index-by-Covariate Interactions

A summary of the significant exposure index-by-covariate interactions is presented in Table 15-11. Two occurred in the officers (one for bradycardia involving an interaction with cholesterol-HDL ratio, and one for ECG-other diagnoses involving an interaction with age) and one in the enlisted groundcrew (for diastolic blood pressure, involving an interaction with personality type).

Longitudinal Analysis

The overall ECG was investigated by longitudinal analysis. The change in status (normal or abnormal) between the 1982 Baseline and 1987 followup examination was determined for each subject participating at both examinations and the degree of change compared in the Ranch Hand and Comparison groups.

Table 15-12 gives summary statistics for the two examinations, as well as summary statistics of the 1985 followup examination for reference purposes. In both groups, the percent with abnormal findings declined from Baseline to the 1985 followup examination, and then increased somewhat at the 1987 followup, although not to the same level as that at Baseline. Table 15-13

TABLE 15-11.

Summary of Exposure Index-by-Covariate Interactions From Adjusted Analyses for Cardiovascular Variables

Variable	Occupation	Covariate	p-Value
Bradycardia	Officer	Cholesterol-HDL Ratio	0.045
ECG-Other Diagnoses	Officer	Age	0.018
Diastolic Blood Pressure	Enlisted Groundcrew	Personality Type	0.012

TABLE 15-12.

Summary Statistics for the Longitudinal Analysis of Overall ECG: 1982 Baseline, 1985 Followup, and 1987 Followup Examinations

Examination	Statistic	Group: Ranch Hand		Group: Comparison	
1982 Baseline	Abnormal	217	26.3%	275	28.2%
	Normal	609	73.7%	701	71.8%
1985 Followup	Abnormal	100	12.3%	127	13.2%
	Normal	712	87.7%	834	86.8%
1987 Followup	Abnormal	132	16.0%	179	18.3%
	Normal	694	84.0%	797	81.7%

Note: Summary statistics for the 1982 Baseline and the 1987 followup are based on 826 Ranch Hands and 976 Comparisons who participated in the 1982 Baseline and 1987 followup examinations. Summary statistics on 812 of these Ranch Hands and 961 of these Comparisons who also participated in the 1985 followup are included for reference purposes only.

TABLE 15-13.

Longitudinal Analyses of the Overall ECG: A Contrast of 1982 Baseline and 1987 Followup Examination Abnormalities

Group	1982 Baseline Exam	1987 Followup Exam: Abnormal	1987 Followup Exam: Normal	Odds Ratio (OR)*	p-Value (OR_{RH} vs. OR_C)
Ranch Hand	Abnormal	66	151	0.437	
	Normal	66	543		0.960
Comparison	Abnormal	103	172	0.442	
	Normal	76	625		

*Odds Ratio: $\frac{\text{Number Normal Baseline, Abnormal 1987 Followup}}{\text{Number Abnormal Baseline, Normal 1987 Followup}}$

presents tables for each of the Ranch Hand and Comparison groups, giving the number of individuals with abnormal ECGs at both the Baseline and 1987 followup examinations, the number abnormal at Baseline but normal at the 1987 followup, etc. Fewer individuals went from normal to abnormal than vice versa, with similar odds ratios in the two groups (p=0.960).

Morbidity-Mortality Analysis

For the cardiovascular evaluation, morbidity and mortality data on all Ranch Hands (diabetics included) and the first Comparison of the randomly ordered set matched to the Ranch Hands were compiled to estimate the frequency of four hierarchical endpoints combining both fatal and nonfatal events. Because of competing mortality and possible misclassification of the cause of death, the endpoints of (1) death (any cause) or verified nonfatal heart disease, and (2) death (any cause) or verified nonfatal myocardial infarction were examined first, followed by endpoints limited to (3) fatal or nonfatal verified heart disease, and (4) fatal or nonfatal verified myocardial infarction or fatal heart disease. The first two endpoints were used to ensure that any misclassification bias with regards to death would not affect the results.

The analysis was based on 1,254 Ranch Hands and 1,249 Comparisons. (Seven Ranch Hands and six Comparisons who had verified heart disease before service in SEA were excluded.) The history of each individual from the beginning of his tour of duty in SEA to the present was then revieved. Histories of verified heart disease and myocardial infarction for living individuals who were noncompliant at Baseline and the two followup visits were missing. For the living noncompliant individuals, the observed rate in the compliant individuals was used to estimate the number of nonfatal events among the noncompliant individuals for each cohort. It was assumed that there were no nonfatal cardiovascular events in the noncompliant individuals who died due to a cause other than cardiovascular system failure. The results are shown in Table L-5 of Appendix L.

There were 85 deaths in the Ranch Hand group and 92 in the Comparisons. The estimated percentage of individuals who died from any cause or had a verified nonfatal history of heart disease (category 1) was 43.6 percent in the Ranch Hands and 43.9 percent in the Comparisons.

The estimated percentage of deaths from any cause or verified nonfatal myocardial infarction (category 2) was 10.0 percent in the Ranch Hands and 11.2 percent in the Comparisons.

Forty-two of the 85 deaths in the Ranch Hands and 41 of the 92 deaths in the Comparisons either were attributed to heart disease or were individuals who had verified heart disease histories. The estimated percentage of fatal and nonfatal verified heart disease (category 3) was 40.1 percent in the Ranch Hands and 39.8 percent in the Comparisons.

Among the 85 deaths in the Ranch Hands, 33 individuals died from cardiovascular disease or had a verified history of myocardial infarction, as compared to 29 of the 92 deaths in the Comparisons. The estimated percentage of fatal or nonfatal verified myocardial infarction or fatal heart disease

(category 4) was 5.9 percent in the Ranch Hands and 6.1 percent in the Comparisons.

These contrasts must be interpreted guardedly since they involve several unverifiable assumptions. Nevertheless, they are consistent with the morbidity findings presented in the chapter and do not indicate excess cardiovascular risk in the Ranch Hands.

DISCUSSION

Of the diseases encountered by the primary care physician, circulatory disorders are among the most common. The sources of the noninvasive data analyzed in the current chapter occupy a time-honored place in cardiovascular practice. Specifically, the history, physical examination, chest x ray, and resting electrocardiogram remain highly reliable indices that can alert the clinician to the presence of underlying cardiovascular disease and point to the need for additional, more specific, noninvasive, or invasive studies. Though arbitrary, dividing data collection into central and peripheral cardiovascular functions is convenient and forms a reasonable basis for comparison of the cohorts under study.

The limitations of the history in cardiovascular diagnosis deserve emphasis. In peripheral vascular disease, for example, signs and symptoms will vary depending on the degree of development of collateral circulatory channels. While hemodynamically significant arterial disease of lower extremities is almost always associated with claudication, severe carotid occlusive disease can be present in the absence of symptoms of transient cerebral ischemia. Further, conclusive evidence shows that advanced coronary artery disease can occur in the absence of angina and present as "silent" myocardial ischemia.[38] Lastly, it is well recognized that the cardiovascular history, as related by patients, is often subject to error. The generic term "heart attack," for example, can be used to describe any type of cardiac event from an isolated episode of unstable angina or arrythmia, to an actual myocardial infarction. These imperfections highlight the importance of the type of medical record verification conducted in the current study.

In the cardiovascular assessment, particularly, the physical examination can provide valuable clues to the presence of asymptomatic but significant underlying disease. Because the examinations were conducted by internists rather than cardiologists, steps were taken to simplify data collection and to reduce interobserver differences among the examining physicians. All blood pressure readings, for example, were taken by automated sphygmomanometric instruments. Auscultory endpoints--murmurs and bruits--were recorded as present or absent by anatomic location, thus eliminating speculation as to specific valvular or vessel origin and hemodynamic significance. As markers of occult arterial occlusive disease, vascular bruits are relatively easy to detect and were carefully sought.

Pertinent to the longitudinal design of the AFHS, several of the physical findings recorded must be viewed in the context of the aging population under study. A gradual increase in systolic blood pressure will occur with advancing years. Related to the normal progression of arteriosclerosis and, more specifically, to arterial tortuosity, vascular bruits may occur in

vessels free of occlusive disease, particularly in the carotid arteries. Again, all bruits were recorded by location without attempting to comment on the hemodynamic significance or specific vessel of origin (i.e., internal vs. external carotid). The occurrence of abnormal heart sounds, particularly S_4, would also be expected to increase with age.

The data collected in the current chapter were limited to the resting 12-lead electrocardiogram and the standard two-view chest x ray. This x ray is used to detect the presence of cardiac enlargement or abnormalities in pulmonary vasculature, as reported in Chapter 20, Pulmonary Disease. In current practice, these techniques are supplemented, but not replaced, by such noninvasive studies as the treadmill exercise test, nuclear isotope studies, and the echocardiogram. With few exceptions, these technically sophisticated and costly procedures do little more than confirm diagnoses that can be made based on data available in the current assessment. For example, when correlated with the history and physical examination, the chest x ray and electrocardiogram enable the clinician to draw highly accurate conclusions regarding the presence and hemodynamic significance of valvular heart disease of any etiology. As defined by the chest x ray, the pulmonary vascularity can provide reliable clues to the presence of global left ventricular dysfunction with pulmonary venous congestion and of pulmonary hypertension of any cause.

The dependent variable-covariate associations analyzed in the current chapter confirm findings that have been well documented in numerous long-term epidemiologic studies. The lack of clearly defined cardiovascular endpoints to dioxin exposure places a premium on the careful analysis of risk factors as potentially confounding variables. More than any other, the cardiovascular system is subject to the effects of lifestyle and heredity.

As a degenerative disease with multiple manifestations, arteriosclerosis develops in all organ systems over time. With few exceptions, an age-related increase in the incidence of abnormal physical findings was documented in both the Ranch Hand and Comparison groups. As expected, reported and verified heart disease and, particularly, previous myocardial infarction, were highly correlated with the classical risk factors of age, positive family history, and cigarette use. Although an apparent exception was the negative correlation between the systolic blood pressure and current cigarette use, this most likely reflects the contributions of former smokers, who have stopped smoking in response to a diagnosed disease. This is the group that had the highest percentage of abnormal systolic blood pressures (above 140 mm Hg). Lifetime cigarette use, on the other hand, was consistently positively associated with abnormalities in all variables analyzed.

The effects of current and lifetime alcohol consumption were less consistent. Clinically, it is clear that in cases of severe, chronic abuse, alcohol is directly cardiotoxic and can lead to an irreversible congestive cardiomyopathy. On the other hand, when consumed in moderation, alcohol may favorably influence the ratio of HDL to LDL cholesterol and may actually be protective with respect to the future development of cardiovascular disease.

Group comparisons generally revealed no significant differences between the Ranch Hand and Comparison cohorts. As in the Baseline examination (but not in the 1985 followup), Ranch Hands had a greater incidence of peripheral pulse abnormalities of the lower extremities than the Comparisons (15.3% vs.

12.2%). As noted above, the 1985 followup included Doppler ultrasound studies, which have proven to be more sensitive than traditional manual palpation. Further analysis of specific pulse sites suggests that the current group difference relates mainly to an increased incidence of femoral, rather than more peripheral, sites, a finding that should be relatively easy to confirm on subsequent examination cycles. Arterial occlusive disease is often unilateral rather than bilateral and can affect large vessels proximally or smaller vessels distally in segmental fashion. Distal circulation may be maintained by good collateral vessels even in the presence of proximal, partial pulse deficits. The Doppler should be more reliable than palpation in such cases, but neither method is perfect. This observed pulse difference does not appear to be related to exposure since abnormalities were not increased in the enlisted groundcrew, the group with the highest serum TCDD levels.

Recently, there has been renewed interest in the role of personality type as a risk factor for cardiovascular disease. In the current study, Type B personality was found to be associated with an increased incidence of elevated systolic blood pressure and with deficits in four of the five peripheral pulses assessed by palpation. Though at variance with classical teaching, these results are consistent with recent evidence that Type B personality may be at equal or greater risk than Type A for the development of coronary artery disease.[39]

In summary, the historical, physical examination, and laboratory data provide a reasonable basis for comparison of the cohorts under study and indicate that neither the Ranch Hand nor the Comparison group is at significant health detriment relative to the other. The slightly greater incidence of heart disease documented in the Ranch Hand cohort in the 1985 followup examination was not evident after continuing review of medical records. The incidence is now similar in the two groups. Finally, as in the Baseline examination (but not in the 1985 followup), a slightly greater incidence of pulse deficits has been found in the Ranch Hand group and will bear continued surveillance in future examination cycles as more accurate methods to measure the body burden of dioxin become available.

SUMMARY

The cardiovascular evaluation of the Ranch Hand and Comparison groups was based upon reported and verified heart disease events (essential hypertension, cardiac disease, and myocardial infarction); assessment of central cardiac function (systolic blood pressure, heart sounds, and ECG findings); and assessment of peripheral vascular function (diastolic blood pressure, funduscopic abnormalities, carotid bruits, and peripheral pulse abnormalities). Table 15-14 presents a summary of all of the unadjusted and adjusted group comparisons for these variables.

In the evaluation of heart disease from questionnaire data, there were no statistically significant differences, unadjusted or adjusted, in the frequency of reported/verified essential hypertension, reported heart disease, or verified heart disease. For reported/verified myocardial infarction, there was no statistically significant difference between the two groups in the unadjusted analysis, but in the adjusted analyses, there was a statistically

TABLE 15-14.

Overall Summary Results of Unadjusted and Adjusted Group Contrast Analyses of Cardiovascular Variables

Variable	Unadjusted	Adjusted	Direction of Results
Questionnaire Variables			
Reported/Verified Essential Hypertension*	NS	NS	
Reported Heart Disease (Excluding Hypertension)	NS	NS	
Verified Heart Disease (Excluding Hypertension)	NS	NS	
Reported/Verified Myocardial Infarction*	NS	** (NS)	
Central Cardiac Function			
Systolic Blood Pressure (continuous)	NS	NS	
Systolic Blood Pressure (discrete)	NS	** (NS)	
Heart Sounds	NS	NS	
ECG-Overall	NS	NS	
RBBB	NS	NS	
LBBB	NS	--	
Nonspecific T-Waves	NS	****	
Bradycardia	0.049	NS*	C>RH
Tachycardia	NS	--	
Arrhythmia	NS	NS*	RH>C
ECG-Other Diagnoses	NS	NS	

TABLE 15-14. (continued)

Overall Summary Results of Unadjusted and Adjusted Group Contrast Analyses of Cardiovascular Variables

Variable	Unadjusted	Adjusted	Direction of Results
Peripheral Vascular Function			
Diastolic Blood Pressure (continuous)	NS*	** (NS*)	RH>C
Diastolic Blood Pressure (discrete)	NS	** (NS)	
Funduscopic Examination	NS	--	
Carotid Bruits	NS*	--	RH>C
Radial Pulses	NS*	--	C>RH
Femoral Pulses	0.016	0.018	RH>C
Popliteal Pulses	NS	NS	
Dorsalis Pedis Pulses	NS*	NS*	RH>C
Posterior Tibial Pulses	NS	****	
Leg Pulses	0.049	NS*	RH>C
Peripheral Pulses	NS*	NS	RH>C
All Pulses	NS*	NS	RH>C

*No conditions reported that were not verified; therefore, reported and verified analyses are the same.

NS: Not significant ($p>0.10$).

** (NS): Group-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Table L-2 for a detailed description of this interaction.

--Adjusted analyses not performed (sparse data).

****: Group-by-covariate interaction ($p\leq0.01$); refer to Table L-2 for a detailed description of this interaction.

NS*: Borderline significant ($0.05<p\leq0.10$).

C>RH: More abnormalities in Comparisons than in Ranch Hands.

RH>C: More abnormalities in Ranch Hands than in Comparisons.

** (NS*): Group-by-covariate interaction ($0.01<p\leq0.05$); borderline significant when interaction is deleted; refer to Table L-2 for a detailed description of this interaction.

significant group-by-family history of heart disease interaction (p=0.042). The relative risk was less than 1 in those with no family history of heart disease and greater than 1 in those with a family history of heart disease; neither within-stratum estimate of risk was statistically significant. An adjusted model fit after deletion of the interaction term was not statistically significant.

For the parameters of central cardiac function there were no statistically significant differences, unadjusted or adjusted, in the mean systolic blood pressure, nor in the percentage of individuals with abnormal heart sounds, overall ECG abnormalities, RBBB, LBBB, tachycardia, or other ECG diagnoses. In the discrete analysis of systolic blood pressure, there was no significant difference between the Ranch Hands and Comparisons in the unadjusted analysis, but a significant group-by-cholesterol-HDL ratio interaction was detected in the adjusted analysis (p=0.020). The adjusted relative risk was less than 1 in those with cholesterol-HDL ratios less than or equal to 4.2 and less than 1 in those with ratios between 4.2 and 5.5, but greater than 1 in those with cholesterol-HDL ratios greater than 5.5. However, none of these within-stratum relative risks was statistically significant, nor was the group comparison after deletion of the interaction term from the model. For nonspecific T-waves, the unadjusted difference was not statistically significant. However, there was a highly significant (p=0.004) group-by-lifetime cigarette smoking history interaction in the adjusted analysis. The relative risk was less than 1 in nonsmokers and moderate lifetime smokers and greater than 1 in heavy smokers. None of these within-stratum risks reached statistical significance. Significantly fewer Ranch Hands than Comparisons had bradycardia (Est. RR: 0.67, 95% C.I.: [0.44,1.00], p=0.049). The adjusted relative risk for bradycardia was borderline significant (Adj. RR: 0.69, 95% C.I.: [0.46,1.04], p=0.068). For arrhythmia there was no significant difference in the unadjusted analysis, but there was a borderline significant difference in the adjusted analysis (Adj. RR: 1.56, 95% C.I.: [0.98,2.49], p=0.062).

In the analysis of peripheral vascular function, no unadjusted or adjusted statistically significant differences were detected in funduscopic abnormalities or in popliteal pulses. The mean diastolic blood pressure was borderline significantly different in the two groups (unadjusted p=0.099); in the adjusted analysis, a significant group-by-age interaction was detected (p=0.028). In individuals born in or after 1942, the Ranch Hand adjusted mean was significantly greater than the Comparison adjusted mean (74.91 vs. 73.56 mm Hg, p=0.026). In those born between 1923 and 1941 and in those born in or before 1922, the adjusted group means were not significantly different. (The difference in the overall adjusted group means was borderline significant [p=0.100] after deleting the interaction term from the model.) The percent with abnormal diastolic blood pressure was not significantly different in the two groups in the unadjusted analysis, but in the adjusted discrete analysis there was a significant group-by-family history of heart disease before age 50 interaction (p=0.043). The relative risk was greater than 1 in those with a family history before age 50 and nearly equal to 1 in those without such a history. The former was of borderline significance (p=0.057) but was based on small numbers (5 of 26 Ranch Hands, 1 of 30 Comparisons). After deletion of the interaction term from the model, the adjusted relative risk was not statistically significant.

There was a borderline significant difference in the percentage of individuals with carotid bruits (Est. RR: 2.97, 95% C.I.: [0.91,9.67], p=0.058). For radial pulse abnormalities, there was also a borderline significant difference; in this case, the estimated relative risk was less than 1 (Est. RR: 0.29, 95% C.I.: [0.06,1.34], p=0.076). Adjusted analyses could not be performed because these abnormalities were so rare.

Both the unadjusted and the adjusted analyses of femoral pulses revealed a significantly greater percentage with abnormalities in the Ranch Hand group than in the Comparison group (p=0.016, unadjusted and p=0.018, adjusted). The estimated relative risk was 2.52 (95% C.I.: [1.16,5.44]) and the adjusted relative risk was 2.52 (95% C.I.: [1.15,5.56]). Both unadjusted and adjusted differences in dorsalis pedis pulses were borderline significant, with a higher percent abnormal in the Ranch Hands than in the Comparisons (Est. RR: 1.30, 95% C.I.: [0.98,1.72], p=0.071 and Adj. RR: 1.29, 95% C.I.: [0.97,1.72], p=0.078). In the case of posterior tibial pulses, there was no significant difference in the unadjusted analyses, but a highly significant group-by-differential cortisol interaction emerged in the adjusted analysis (p=0.004). There was little group difference in those with differential cortisol response less than or equal to 0.6, but the risk was significantly greater than 1 in those with differential cortisol levels between 0.6 and 4.0 (Adj. RR: 3.04, 95% C.I.: [1.06,8.68], p=0.030). The relative risk was less than 1 and not statistically significant in those with differential cortisol response greater than 4.0. In the variable combining all leg pulses, the Ranch Hands exhibited significantly more abnormalities than the Comparisons (Est. RR: 1.30, 95% C.I.: [1.00,1.67], p=0.049). The adjusted relative risk for leg pulses was of borderline significance (p=0.079). For peripheral pulses, the estimated relative risk was borderline significant (Est. RR: 1.26, 95% C.I.: [0.97,1.62], p=0.082). This was also the case for all pulses (Est. RR: 1.26, 95% C.I.: [0.97,1.62], p=0.081).

There was agreement between the physical examination findings and the past medical history, with a number of positive and statistically significant associations detected between various physical parameters and the heart disease history.

Exposure index analyses conducted within the Ranch Hand group did not detect any significant effects in any of the three occupational cohorts for reported/verified essential hypertension, reported/verified myocardial infarction, heart sounds, overall ECG findings, RBBB, LBBB, tachycardia, funduscopic examination findings, and carotid bruits, nor in any of the pulse variables or pulse aggregates. For reported and verified heart disease, there were no significant differences in the enlisted flyers or enlisted groundcrew. In the officers, the group with the lowest current serum TCDD levels, the adjusted medium versus low exposure level contrast was significantly less than 1 (p=0.019), and the high versus low contrast was also less than 1 and of borderline significance (p=0.082).

No significant differences were detected in the analysis of systolic blood pressure in the officers and enlisted groundcrew, but in the enlisted flyers there was a significant difference in the means that was consistent with a dose-response relationship (p=0.037)--mean values were 124.14, 128.79, and 133.55 in the low, medium, and high exposure level categories, respectively. After covariate adjustment, however, the differences were no

longer statistically significant (p=0.181). There were no statistically significant differences in nonspecific T-wave findings in the officers or enlisted groundcrew. Although not entirely consistent with a dose-response relationship, there was a borderline significant difference in the enlisted flyers (p=0.075, unadjusted and p=0.091, adjusted).

No statistically significant exposure level effects were detected in the unadjusted analyses of bradycardia, nor in the adjusted analyses within the enlisted flyers or enlisted groundcrew. In the officers, however, a significant exposure index-by-cholesterol-HDL ratio interaction was detected (p=0.045). Upon stratification, there were fewer abnormalities in the medium and high exposure level categories than in the low exposure level category for those with cholesterol-HDL ratios less than or equal to 4.2 and for those with levels between 4.2 and 5.5, but slightly more abnormalities in the medium and high exposure level categories as compared to the low category for those with ratios greater than 5.5. These were all based upon small numbers.

For arrhythmia, there were no significant differences in the officers or enlisted groundcrew, but in the enlisted flyers, there were six abnormalities in the high exposure level category as compared to none in the low category and none in the medium category (p=0.025 for the high vs. low contrast). Adjusted analyses could not be performed due to the small numbers. For other ECG diagnoses, no significant differences were found except for a significant exposure index-by-age interaction in the officer cohort (p=0.018). The differences within each of the age strata were not consistent with a dose-response relationship, however. Finally, there were no significant exposure level effects on diastolic blood pressure in the enlisted flyers. In the officers, there was a significantly greater percentage of abnormalities in the higher exposure level category as compared to the low exposure level category (p=0.039), but there was no excess risk in the medium exposure level group. Also, in the enlisted groundcrew there was a significant exposure index-by-personality type interaction (p=0.012), but the within-stratum differences were not consistent with a dose-response relationship.

Longitudinal analysis of the overall ECG findings did not detect any significant differences between the Ranch Hand and Comparison groups in the change in the overall ECG status from Baseline to the 1987 followup examination. Mortality-morbidity analyses did not indicate excess cardiovascular risk in the Ranch Hands.

In summary, the cardiovascular evaluation showed that the health of the Ranch Hand and Comparison groups was similar for reported and verified heart disease and central cardiac function. For peripheral vascular function, the Ranch Hands had a marginally higher percentage of individuals with carotid bruits. There were also significant, or marginally significant, differences (more abnormalities in the Ranch Hands than in the Comparisons) in femoral pulses, dorsalis pedis pulses, and in the three pulse aggregates (leg, peripheral, and all pulses), as determined by manual palpation. These findings emphasize the importance of including further evaluations of peripheral pulses in subsequent examinations in this study.

CHAPTER 15

REFERENCES

1. Canga, L., R. Levi, and A.B. Rifkind. 1988. Heart as a target organ in 2,3,7,8-tetrachlorodibenzo-p-dioxin toxicity: Decreased beta-adrenergic responsiveness and evidence of increased intracellular calcium. Proc. Natl. Acad. Sci. 85(3):905-909.

2. Hermansky, S.J., T.L. Holcslaw, W.J. Murray, R.S. Markin, and S.J. Stohs. 1988. Biochemical and functional effects of 2,3,7,8-tetrachloro-dibenzo-p-dioxin on the heart of female rats. Toxic. Appl. Pharmacol. 95(2):175-184.

3. Brewster, D.W., F. Matsumura, and T. Akera. 1987. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on guinea pig heart muscle. Toxic. Appl. Pharmacol. 89(3):408-417.

4. Kelling, C.K., L.A. Menahan, and R.E. Peterson. 1987. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin treatment on mechanical function of the rat heart. Toxic. Appl. Pharmacol. 91:497-501.

5. Brewster, D.W., D.W. Bommbick, and F. Matsumura. 1988. Rabbit serum hypertriglyceridemia after administration of 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD). J. Toxicol. Environ. Health 25(4):495-507.

6. Serabjit-Singh, C.J., J.R. Bend, and R.M. Philpot. 1985. Cytochrome P-450 monooxygenase system. Localization in smooth muscle of rabbit aorta. Mol. Pharmacol. 28(1):72-79.

7. Janicki, P.K., E.A. Paulo, W. Pasierbski, Z. Rutczynska, and Z. Szreniawski. 1986. An interaction between herbicides and most frequently used group of drugs I. Interaction of chronically administered herbicides carbendazim 2,4-D and 2,4,5-T with drugs affecting cardiovascular system. Med. Pr. 37(3):167-174.

8. Palmer, J.S., and R.D. Radeleff. 1964. The toxicologic effects of certain fungicides and herbicides on sheep and cattle. Ann. N.Y. Acad. Sci. 111:729-736.

9. McConnell, E.E., J.A. Moore, and D.W. Dalgard. 1978. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Rhesus monkeys (Macaca mulatta) following a single oral dose. Toxicol. Appl. Pharmacol. 43(1):175-187.

10. Kimbrough, R.D., C.D. Carter, J.A. Liddle, R.E. Cline, and P.E. Phillips. 1977. Epidemiology and pathology of a tetrachlorodibenzodioxin poisoning episode. Arch. Environ. Health 32(2):77-86.

11. McConnell, E.E., J.A. Moore, J.K. Haseman, and M.V. Harris. 1978. The comparative toxicity of chlorinated dibenzo-p-dioxins in mice and guinea pigs. Toxicol. Appl. Pharmacol. 44(2):335-356.

12. Schreiweiss, D.O., and G.J. Murray. 1976. Cardiovascular malformations in Oryzias latipes embryos treated with 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Teratology 14(3):287-290.

13. Rifkind, A.B., Y. Hattori, R. Levi, M.J. Hughes, C. Quilley, and D.R. Alonso. The chick embryo as a model for PCB and dioxin toxicity: Evidence of cardiotoxicity and increased prostaglandin synthesis. In Banbury report 18: Biological mechanisms of dioxin action, ed. A. Poland and R.D. Kimbrough, pp. 255-266. Cold Spring Harbor, New York: Cold Spring Harbor Laboratory.

14. Quilley, C.P., and A.B. Rifkind. 1986. Prostaglandin release by the chick embryo heart is increased by 2,3,7,8-tetrachlorodibenzo-p-dioxin and by other cytochrome P-448 inducers. Biochem. Biophys. Res. Commun. 136(2):582-589.

15. Dudley, A.W., and N.T. Thapar. 1972. Fatal human ingestion of 2,4-D, a common herbicide. Arch. Path. 94:270-275.

16. Paggiaro, P.L., E. Martino, and S. Mariotti. 1974. A case of 2,4-dichlorophenoxyacetic acid (2,4-D) poisoning. Med. Lavoro 65(3-4): 128-135.

17. Berwick, P. 1970. 2,4-dichlorophenoxyacetic acid poisoning in man. JAMA 214(6):1114-1117.

18. Oliver, R.M. 1975. Toxic effects of 2,3,7,8-tetrachlorodibenzo-1,4-dioxin in laboratory workers. Br. J. Ind. Med. 32:46-53.

19. Baader, E.W., and A.J. Bauer. 1951. Industrial intoxication due to pentachlorophenol. Ind. Med. Surg. 20:289-290.

20. Jirasek, L., J. Kalensky, K. Kubec, J. Pazderova, and E. Lukas. 1974. Acne chlorina, porphyria cutanea tarda and other manifestations of general intoxication during the manufacture of herbicides, part 2. Czech. Dermatol. 49(3):145-157.

21. Pazderova-Vejlupkova, J., M. Nemcova, J. Pickova, L. Jirasek, and E. Lukas. 1981. The development and prognosis of chronic intoxication by tetrachlorodibenzo-p-dioxin in men. Arch. Environ. Health 36:5-11.

22. Poland, A.P., D. Smith, G. Metter, and P. Possick. 1971. A health survey of workers in a 2,4-D and 2,4,5-T plant, with special attention to chloracne, porphyria cutanea tarda, and psychologic parameters. Arch. Environ. Health 22(3):316-327.

23. Durakovic, Z. 1985. Intoxication by 2,4-D herbicide, followed with coma and prolonged Q-T interval in the electrocardiogram. Rad. Med. Fak. Zagrebu. (Yugoslavia) 26(1):51-54.

24. Moses, M., R. Lilis, K.D. Crow, J. Thornton, A. Fischbein, H.A. Anderson, and I.J. Selikoff. 1984. Health status of workers with past exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin in the manufacture of 2,4,5-trichlorophenoxyacetic acid: Comparison of findings with and without chloracne. Am. J. Ind. Med. 5:161-182.

25. Suskind, R.R., and V.S. Hertzberg. 1984. Human health effects of 2,4,5-T and its toxic contaminants. JAMA 251:2372-2380.

26. Hoffman, R.E., P.A. Stehr-Green, K.B. Webb, G. Evans, A.P. Knutsen, W.F. Schramm, J.L. Staake, B.B. Gibson, and K.K. Steinberg. 1986. Health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. JAMA 255:2031-2038.

27. Stehr, P.A., G. Stein, H. Falk, E. Sampson, S.J. Smith, K. Steinberg, K. Webb, S. Ayres, and W. Schramm. 1986. A pilot epidemiologic study of possible health effects associated with 2,3,7,8-tetrachlorodibenzo-p-dioxin contamination in Missouri. Arch. Environ. Health 41:16-22.

28. Lathrop, G.D., S.G. Machado, T.G. Karrison, W.D. Grubbs, W.F. Thomas, W.H. Wolfe, J.E. Michalek, J.C. Miner, M.R. Peterson, and R.W. Ogershok. 1987. Epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides: First followup examination results, NTIS: AD A 188 262. USAF School of Aerospace Medicine, Human Systems Division, Brooks Air Force Base, Texas.

29. Pollei, S., F.A. Mettler, C.A. Kelsey, M.R. Walters, and R.E. White. 1986. Follow-up chest radiographs in Vietnam veterans: Are they useful? Radiology 161:101-102.

30. Troxler, R.G., and H.A. Schwertner. 1985. Cholesterol, stress, lifestyle, and coronary heart disease. Aviat. Space Environ. Med. 56:660-665.

31. American Heart Association Steering Committee for Medical and Community Program. 1980. Risk factors and coronary disease: A statement for physicians. Circulation 62:449A-455A.

32. Castelli, W.P. 1984. Epidemiology of coronary heart disease: The Framingham study. Am. J. Med. 76:4-12.

33. Multiple Risk Factor Intervention Trial Research Group (Neaton, J.D., L.H. Kuller, D. Wentworth, and N.O. Borhani). 1984. Total and cardiovascular mortality in relation to cigarette smoking, serum cholesterol concentration, and diastolic blood pressure among black and white males followed for five years. Am. Heart J. 108:759-769.

34. Lipid Research Clinic Program: The Lipid Research Clinic's Coronary Prevention Trial Results: II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. 1984. JAMA 251:365-374.

35. Stamler, J., D. Wentworth, and J.D. Neaton. 1986. Is relationship between serum cholesterol and risk premature death from coronary heart disease continuous and graded? JAMA 256:2823-2828.

36. Martin, J.V. 1984. Lipid abnormalities in workers exposed to dioxin. Br. J. Ind. Med. 41:254-256.

37. Ashe, W.F., and R.R. Suskind. 1949, 1950. Reports on chloracne cases, Monsanto Chemical Company, Nitro, West Virginia. In Report of the Kettering Laboratory, December 1949 and April 1950.

38. Chatterjee, K. 1989. Ischemia--silent or manifest: Does it matter? Am. J. Cardiology 13:1503-1505.

39. Ragland, D.R., and R.J. Brand. 1988. Type A behavior and mortality from coronary heart disease. N. Engl. J. Med. 318:65-69.